

REMARKS

In response to the Office Action dated September 17, 2009, Claims 1 and 13 have been amended to more clearly recite the subject matter. Support for these amendments can be found throughout the specification, more particularly, from page 12, lines 24-26, page 13, lines 5-24, page 25, lines 10-14 and page 37, lines 20-21 of the originally filed specification. Claims 1, 2-4, 9, 10, and 12-14 have been amended to correct informalities. Claims 17 and 18 have been canceled without prejudice. New Claims 43 and 44 have been added and support for the new claims can be found from the original Claims 1 and 13. No new matter has been added in this response. Currently Claims 1-16, 43, and 44 remain pending and Claims 1-13, 15, 16, 43, and 44 are presented for the Examiner's consideration.

Sequence listing

Applicants received a notice to comply with requirements for patent application containing nucleotide sequence and/or amino acid sequence disclosure along with the office action. A complete response to the notice including the sequence listing in a computer readable form (CRF) that is in compliance with the requirement of 37 CFR 1.821 to 1.825 and the sequence submission statement was filed on October 9, 2009 in reply to the notice.

With this response, Applicants submit a substitute Sequence Listing. In this substitute Sequence Listing, SEQ ID Nos. 12-16 have been amended and new SEQ ID Nos. 144-148 have been added to correctly reflect the amino acid sequences shown in Figure 5, page 2 of the original application. The substitute specification filed herewith includes an amendment to provide reference to the substitute sequence listing submitted herewith.

As set forth in the Federal Register Notice of October 27, 2009 (74 FR 55209), the ASCII text file of the Sequence Listing filed herewith "will serve as both the paper copy required by 37 CFR 1.821(c) and the computer readable form (CRF) required by 37 CFR 1.821(e)." Accordingly, pursuant to the same Federal Register Notice, neither of the following are being submitted: "(1) A second copy of the sequence listing in a PDF file; [or] (2) a statement under 37 CFR 1.821(f) (indicating that the paper copy and CRF copy of the sequence listing are identical)."

In addition, since an amendment to, or a replacement of, a sequence listing (under 37 CFR 1.821(c) and (e)) is submitted as an ASCII text file via EFSWeb, the undersigned also confirms that: (1) the submission does not include any new matter which goes beyond the disclosure of the

application as filed, and (2) support for the amendment is present in the application, as filed at Figure 5, page 2.

Figure 5, page 2 shows the alignment of two regions of amino acid sequences. The sequences corresponding to the first region, from Gln (Q) 73 to Leu (L) 98 of PDK1, are shown in the upper block and those corresponding to the second region, from Arg (R) 129 to Glu (E) 153 of PDK1, are shown in the lower block. The sequences disclosed in the upper and lower blocks may not be continuous; however, the original SEQ ID Nos. 12-16 show these aligned sequences as continuous sequences. To correctly reflect the sequences shown in Figure 5, SEQ ID Nos. 12-16 have been amended to show the sequences of the upper block. New SEQ ID NOs. 144-148 now show the sequences of the lower block. As such, no new matter is being added in the substitute Sequence Listing, which is recorded in computer readable form and filed herewith.

In view of the foregoing, the substitute Sequence Listing is in compliance with the requirement of 37 CFR 1.821 to 1.825. Applicants hereby direct entry of the substitute Sequence Listing submitted herewith into the present application.

Objections to the Specification

The specification was objected to for the following informalities:

- (1) the title is not descriptive;
- (2) the abstract contains legal terms, exceeds 150 words and should be on a separate sheet;
- (3) nucleotide sequences of at least 10 nucleotides and amino acid sequences of at least 4 amino acids in the specification should be identified by a proper sequence identifier;
- (4) the amino acid sequences in the Examples 2, 3, 4, and 7 should be identified; and
- (5) the specification contains an embedded hyperlink and/or other form of browser-executable code.

All of the above-mentioned informalities have been properly addressed by the amendments made in this response. More particularly, the title has been amended as set forth above. The Abstract has been amended and is now submitted in a separate sheet, which is the last page of this response. In addition, Applicants submit a substitute specification, which includes sequence identifiers at proper places but lacks hyperlink and/or other form of browser-executable code, herewith. Regarding the hyperlink that is “<http://davapc1.bioch.dundee.ac.uk/programs/prodrg/prodrg.html>” on page 14, lines 14 of the original specification, the

hyperlink was removed and “Daan van Aalten Laboratory”, which is directed by the removed hyperlink, is cited. The identity of the amino acid sequences in the Examples 2, 3, 4, and 7 are described in page 7, lines 14-23 and page 8, lines 4-7 of the substitute specification filed herewith. In accordance with MPEP 608.01(a), a Brief Description of the Drawings has been added to the specification, support for which can be found in the specification as filed under the heading “Figure legends,” on pages 41-44 of the specification as filed. The section headings for the various parts of the application set forth in MPEP 608.01(a) have also been added.

In light of the foregoing amendments, Applicants respectfully request withdrawal of objections to the specification.

Objections to the Claims

Claims 3 and 4 were objected to for allegedly improperly broadening the scope of Claim 1, which they depend from. This objection appears to be due to the closed term “consisting” in Claim 1, which was used to describe a polypeptide. In order to expedite the prosecution, Applicants have amended Claim 1 to recite a polypeptide comprising residues equivalent to residues 51 to 359 of full length human PKK1 (SEQ ID NO. 3), or a fragment or fusion thereof. Thus it is believed that the objection to Claims 3 and 4 is no longer applicable. Withdrawal of this claim objection is respectfully requested.

Claims 9 and 11-13 were also objected to due to other informalities. As set forth above, the noted informalities in the Office Action have been removed by the current amendments. In light of the amendments, Applicants respectfully request cancellation of the objections to Claims 9 and 11-13.

Rejections to Claims 1-13 and 15-18 under 35 U.S.C. 112, second paragraph (indefiniteness)

Claims 1 and 13 were rejected due to the term “modelling means”, which is allegedly unclear and indefinite according to the Examiner. By the amendments to Claims 1 and 13 in this response, such term is no longer present in the claims. Accordingly, this rejection is now moot.

Claims 1, 10, and 13 were rejected due to the phrase “residues equivalent to”, “equivalent residues” or “position equivalent to”, which is allegedly unclear and indefinite. Applicants respectfully submit that the meaning of “equivalent” cited in the foregoing phrases would be abundantly apparent to the skilled person in the art. As is immediately evident from page 24, line

28 to page 25, line 13 of the present specification, one with ordinary skill in the art can determine the residue equivalent to a given residue by aligning sequences in the manner set forth in this passage of the specification. Identity is not required, as would be well known to the skilled person and as is set out on page 23, line 27 to page 24, line 19 of the present specification. Accordingly, it is believed that the noted phrases with the term “equivalent” in Claims 1, 10, and 13 are clear and definite. Withdrawal of the rejection is respectfully requested.

Claims 13 and 15 were rejected due to the phrase “hydrophobic pocket”, which is allegedly unclear and indefinite. The noted phrase has been replaced with the phrase “PIF binding pocket” and the meaning of “PIF binding pocket” is clearly described in the specification, for examples in page 3, lines 9-24, page 46, line 16 to page 7 line 19, Figure 2 and Example 1 of the originally filed application, as well as set out in the claims. Accordingly, withdrawal of the rejection is respectfully requested.

Claims 1-4 were rejected due to the parenthesis present in the claims. Claims have been amended and no parenthesis is present in the claims. Thus this rejection is now moot.

Claims 1-4, 10, and 13 were rejected due to lack of sequence identifiers for the sequences recited therein. As sequence identifiers have been incorporated into the claims, this rejection is also now moot.

Claim 9 was rejected due to the phrase “represented by the structure co-ordinates shown in Examples...”, which was allegedly unclear and indefinite. Applicants respectfully traverse this rejection and submit that the structure co-ordinates are a well-known way of representing or describing the structure in the art. The structure could alternatively be represented as a picture or a diagram but in the present application is represented by a listing of structure co-ordinates. It is evident to a person with ordinary skill in the art that this claim is limited to the structure being the one that is described (i.e. represented) by the structure co-ordinates shown in Examples 2, 3, 4, 7, or 8 of the specification. Therefore, in light of the remarks, withdrawal of the rejection is respectfully requested.

Claim 10 was rejected due to the parenthesis in the claim. The parenthesis has been removed from the claim and thus this rejection is now moot.

Claim 11 was rejected due to the phrase “other PH-domain”, which is allegedly unclear and indefinite. Applicants respectfully traverse this rejection. What Claim 11 recites, among

others, other PDK1 substrate that comprises PH-domain. The term “pleckstrin homology or PH-domain” is well known in the art (e.g. as described in the attached article from http://en.wikipedia.org/wiki/Pleckstrin_homology_domain) (downloaded January 15, 2010), as well as clearly described in the originally filed specification (*See* page 1, lines 16-17 of the specification). As such, Claim 11 would be abundantly clear to the skilled person in the art and thus rejection to Claim 11 is respectfully requested.

Claim 12 was rejected due to the phrase “other substrate of PDK1”, which is allegedly unclear and indefinite. However, Claim 12 expressly describes the parameters of the noted phrase. It recites, among others, that “other substrate of PDK1” encompass any substrate of PDK1 whose phosphorylation by PDK1 is promoted by phosphorylation of the substrate on the Ser/Thr of the “hydrophobic motif” FXXFS/TY (SEQ ID NO. 2). The noted phrase and the accompanying description in Claim 12 should be apparently clear to one with ordinary skill in the art. As such, it is believed that what is claimed in Claim 12 is clear and definite. Reconsideration of Claim 12 is respectfully requested.

Claim 13 was rejected due to the phrase “(PIF binding protein)”. The noted phrase is allegedly with respect to whether the recitation insider the parenthesis should be considered as claim limitation or not. Claim 13 has been amended to remove the allegedly unclearness and thus the rejection is now moot.

Claims 17 and 18 were rejected. While Applicants disagree with these rejections in order to advance prosecution, Claims 17 and 18 have been canceled. Thus the rejection to these claims is now moot.

Rejections to Claims 1-13 and 15-18 under 35 U.S.C. 112, second paragraph (omission of essential steps)

Claims 1-13 and 15-18 were rejected under 35 U.S.C 112, second paragraph, as allegedly being incomplete for omitting essential steps. Applicants respectfully traverse the rejection.

Claims 1 and 13 have been amended and now recite, among other elements, modelling a three-dimensional structure of a plurality of molecules in a computer, comparing a three dimensional structure with one or more of references structures (i.e. a three-dimensional structure of at least a part of the protein kinase catalytic domain of PDK1 in Claim 1; or a three-dimensional structure of the phosphate binding pocket and optionally also the hydrophobic pocket

and/or α C helix or region interacting therewith in Claim 13), and selecting said compound based on a predicted ability of the molecules to interact with the reference structures.

In the Office Action, the Examiner asserted that some “wet” biochemical assays to determine the protein kinase or the activation state of a protein kinase would be necessarily included to the claimed method. While such assaying steps can be further added to the method in some specific occasions, which is also disclosed in the application, these assays would not be necessary in every occasion to select the desired compound. As described above, modelling can be done via a computer-based system and the steps of comparing and selecting can also be done via a computer or any other methods, which may include, but are not limited to, the “wet” biochemical assays. That is, the claimed method according to Claims 1 and 13 certainly encompasses the method operated with and without the biochemical assays and thus adding limitations particularly related to the biochemical assays would be unnecessarily narrow the scope of the invention.

As noted, Applicants believe the currently presented Claims 1 and 13 recite the complete and essential steps for the claimed method. In light of these remarks, withdrawal of the rejection to Claims 1 and 13 and their dependent claims is respectfully requested.

Rejections to Claims 1-13 and 15-18 under 35 U.S.C. 112, first paragraph (enablement)

Claims 1-13 and 15-18 were rejected under 35 U.S.C. 112, first paragraph, as allegedly failing to provide enablement. More particularly, it is asserted by the Examiner that to practice the claimed invention, the skilled person would be required to carry out undue experimentation. Applicants respectfully disagree with this assertion and submit that the specification is enabling across the entire scope of the claims.

In the office Action, the Examiner has cited *In re Wands* as basis for objecting that undue experimentation will be required to practice the whole scope of the invention. The aspects of that case that the examiner appears to consider important in reaching this conclusion are: A) the breadth of the claims; B) the state of the art, the level of one of the ordinary skill and the level of predictability; C) the amount of direction provided by inventor; and D) the quantity of experimentation needed. Applicants however respectfully disagree with the rejection for the reasons as described below.

A) In the light of the above arguments and/or amendments, Claim 1 is limited to the use of the 3D structure of the catalytic domain of PDK1, specifically those residues equivalent to 51 to 359 of full length human PDK1, and not any part of the catalytic domain. The same logic applies to Claim 13. The skilled person would appreciate that crystallizing the equivalent region of a protein, when the present application provides a template for such crystallization, would be predictable. The skilled person would have a high expectation of success and would not need to get involved in undue experimentation. Clearly, the experimental parameters provided in the present application may be used to crystallize, with a high expectation of success, a homologous protein region for use in the methods of the present claims.

B) The Examiner considers the prior art to indicate that there was a high level of unpredictability for making and using x-ray diffraction quality protein crystals at the time of the invention. The Branden *et al* publication does suggest that crystallization is usually difficult to achieve; but, this document relates to producing a crystal from scratch and not the situation of the present application where the inventors have provided the structure of the relevant regions of PDK1 to be used as a reference structure to produce structures of other homologues of these regions. Also, Branden is a textbook published in 1999, 3-4 years before the present application. In such a fast moving field as crystallography, textbooks are generally out of date before they are published, let alone 4 years later. Given the Examiner's incorrect analysis of the breadth of the claims and the lack of relevance of Branden to the facts of the present case, Branden does not indicate that the present claims are not enabled. Further, the Examiner has cited Drenth *et al*, an even older textbook published in 1995, to indicate that crystallization is a "trial and error process". However, as discussed above, no trial and error would be required in view of the disclosure provided in the present application. Accordingly, Drenth is not relevant for the assessment of the enablement of the claims of the present application.

The Examiner has also cited a more contemporary review, Kierzek *et al* (2001). Kierzek suggests that crystallization conditions must be established for each protein to be crystallized. Nevertheless, Kierzek also relates to crystallization of unknown proteins in general. The facts of the present case are different. In the present application, a small region, homologous with an already crystallized reference sequence, is used to produce crystals for molecular modelling.

There is no reason to suspect that the conditions provided in the present application would not be suitable for crystallizing proteins falling within the scope of Claims 1 and 13.

A yet further review, Wiencek *et al* (1999), has been cited by the Examiner to suggest that protein solubility will change with changes in pH. Again, Wiencek is concerned with protein crystallization in general and conditions affecting such; and is not concerned with small protein, homologous with an already crystallized protein.

The Examiner has also cited Lambert *et al* (US 2004/0137518), allegedly suggesting that available homology models were not able to provide the necessary degree of specificity for the *in silico* design of modulators. The quote in the Office Action from Lambert has been taken out of context. The authors clearly consider a crystal structure to be an appropriate means for *in silico* modelling of modulators into the active site of the protein. They discuss methods of homology modelling absent the relevant crystal structure, to provide a lower degree of specificity.

The Examiner considers the specification to be enabling for modelling modulators with the exemplified crystal structure, so it does not follow that the modelling step could not easily be carried out with further crystal structures. The specification is clearly enabling across the proper scope of the claims.

C) As indicated above, the skilled person would consider that the amount of direction provided by the inventor and the working examples in the specification would be sufficient to allow the methods of the properly construed claims to be carried out.

D) As can be seen, the skilled person would not be presented with the need to carry out undue experimentation in order to perform the methods of the invention.

As noted above, Applicants respectfully submit that upon the proper construction of the claims that should result from the comments in relation to the preceding objections, the present claims are fully enabled by the specification. Accordingly, withdrawal of the rejection under this section and favorable consideration of the pending claims is respectfully requested.

Rejections to Claims 1-13 and 15-18 under 35 U.S.C. 112, first paragraph (written description)

Claims 1-13 and 15-18 were rejected under 35 U.S.C. 112, first paragraph, for allegedly failing to comply with the written description requirement. Applicants respectfully traverse the rejection.

This rejection appears to have arisen partly due to the Examiner's broad interpretation of the proteins referred to in the claims (as a result of the objection of lack of clarity), and partly due to the Examiner's view that protein crystallization and rational drug design is an inherently unpredictable field. As discussed above, however Claims 1 and 13 specifically recite a method of selecting a compound based on its predicted ability to interact with a three-dimensional structure of at least a part of the protein kinase catalytic domain of PDK1 as in Claim 1, or a three-dimensional structure of the phosphate binding pocket and optionally also the hydrophobic pocket and/or α C helix or region interacting therewith as in Claim 13. The detailed structure, physical and/or chemical characteristics of each of the reference structures are well disclosed in the specification. For example, see pages 45 to 51 of the originally filed specification. Further the 3D structure, x-ray crystallography data and the amino acid sequence of each reference are well disclosed throughout the specification.

Moreover, as also discussed above, protein crystallization and rational drug design is a highly predicted field as supported by the prior art, for example, Lambert *et al* (US 2004/0137518). In addition, the specification via Examples demonstrates the practicality of the claimed method including crystallization methods and the resulting data as an exemplary illustration. More particularly, Applicants provide sufficient written description of the claimed method using the case of UCN-01, a derivative of staurosporine in the specification. Conventionally UCN-01 was considered to have similar or same activity to staurosporine in PDK1 inhibition due to the similarity in structure. Applicants however clearly demonstrate in the specification that there is significant difference in UCN-01 activity from staurosporine and such difference is due to the predicted binding ability of UCN-01 to PDK1. UCN-01 comprises 7-hydroxyl group, which is not present on staurosporine, and this group indeed show different interaction pattern to PDK1 as compared to staurosporine as disclosed in Figure 9 and Table 4 of the present application.

With such description readily available in the specification, a skilled person in the art would be readily able to convey that the applicants at the time of the application was fielded had possession of the claimed invention. Accordingly, withdrawal of the rejection under this section is respectfully requested.

Rejection of Claims 17-18 under 35 U.S.C. 102(b)

Claims 17-18 were rejected under 35 U.S.C. 012(b) as allegedly being anticipated by Godden et al. (Evaluation of docking strategies for virtual screening of compound database: cAMP-dependent serine/threonine kinase as an example, Journal of Molecular Graphics and Modelling, Volume 16, Issue 3, June 1998, Pages 139-143). Applicants have canceled Claims 17 and 18 solely to advance prosecution. Thus the rejection is now moot.

Rejection of Claims 1-13 and 15-18 under 35 U.S.C. 103(a)

Claims 1-13 and 15-18 were rejected under 35 U.S.C. 013(a) as allegedly being unpatentable over Brown et al. (The structural basis for specificity of substrate and recruitment peptides for cyclin-dependent kinases, Nat Cell Biol. 1999, Nov: Vol. 1, No. 7, pp:438-443) in view of *In re Gulack* 217 USPQ 401 (Fed. Cir. 1983). Applicants respectfully traverse the rejection.

It was asserted by the Examiner in the Office Action that by virtue of being kinase, CDK2 disclosed in Brown inherently possesses “protein kinase catalytic domain”, “phosphate binding pocket”, and “hydrophobic pocket”. See page 31, lines 3-5 of the Office Action. Based on this assertion, the Examiner appears to understand Brown reference would inherently disclose at least some claimed method of the present application. Applicants however respectfully submit that the Examiner’s assertion is incorrect. CDK2 is a protein kinase that does not possess a hydrophobic pocket or a PIF binding pocket. See page 25, lines 15-21 of the present application. As such, the Examiner’s rejection is based on an incorrect assertion. Moreover, the Brown reference observed the interaction of synthetic peptide to the binary complex of CDK2-cyclin A3, whereas the present invention involves modelling the compound based on its potential interaction with a specific reference portion of the kinase (i.e. a three-dimensional structure of at least a part of the protein kinase catalytic domain of PDK1 in Claim 1; or a three-dimensional structure of the phosphate binding pocket and optionally also the hydrophobic pocket and/or α C helix or region interacting therewith in Claim 13). Therefore, Applicants respectfully submit that the disclosures in Brown reference cannot teach or suggest the presently claimed invention.

The Examiner correctly acknowledged that Brown is deficient in teaching the atomic coordinates as set forth in Examples, 2-4, 7, and 8. However, in light of *In re Gulack*, the Examiner asserted that the atomic coordinates are nonfunctional descriptive material and such materials cannot render the invention nonobvious. However, the Examiner has misconstrued the

holding of *In re Gulack*. The full decision is reported at 217 U.S.P.Q. 401 (Fed. Cir. 1983). In fact, as described below, the decision actually supports the patentability of the claims reciting the atomic coordinates.

The Federal Circuit relied on its earlier decision in *In re Miller*, which it characterized as holding that “[d]ifferences between an invention and the prior art cited against it cannot be ignored merely because those differences reside in the content of the printed matter,” which was alleged to be nonstatutory subject matter. *Id.* at 403. “Under section 103, the board cannot dissect a claim, excise the printed matter from it and declare the remaining portion of the mutilated claim to be unpatentable. The claim must be read as a whole.” *Id.*

The Federal Circuit acknowledged that “where the printed matter is not functionally related to the substrate, the printed matter will not distinguish the invention from the prior art in terms of patentability.” *Id.* at 404. However, in the *Gulack* decision, the Federal Circuit concluded that Gulack’s claimed “digits imprinted on the band or ring at regularly spaced intervals” were “functionally related to the band” and concluded that the prior art did not disclose the recited digits. For that reason, the Federal Circuit held that Gulack’s claims were nonobvious. *Id.*

In the present case, the atomic coordinates are functionally related to the computer on which they are modeled, and must be considered as material to the patentability of the claims. As discussed above, the representation of structure of a compound via atomic coordinates is well known in the art as one of variety of ways of illustrating the compound structure. Once the structure is determined, the function is inherently determined according to the compound structure, especially for many biologically active compounds. Moreover in the claimed method, the material is indeed functional as it is this material that allows selection of compounds that are predicted to interact with the particular protein kinase under consideration.

In light of the foregoing remark, Applicants respectfully submit that Claims 1-13 and 15 are nonobvious over Brown, and further in view of *In re Gulack*. Accordingly reconsideration of the patentability of the claims is respectfully requested.

No Disclaimers or Disavowals

Although the present communication may include alterations to the application or claims, or characterizations of claim scope or referenced art, Applicant is not conceding in this

application that previously pending claims are not patentable over the cited references. Rather, any alterations or characterizations are being made to facilitate expeditious prosecution of this application. Applicant reserves the right to pursue at a later date any previously pending or other broader or narrower claims that capture any subject matter supported by the present disclosure, including subject matter found to be specifically disclaimed herein or by any prior prosecution. Accordingly, reviewers of this or any parent, child or related prosecution history shall not reasonably infer that Applicant has made any disclaimers or disavowals of any subject matter supported by the present application.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

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